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Antihypertensive Action of Benzothiadiazines

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CHLOROTHIAZIDE and other diuretics of similar structure have become established as valuable therapeutic agents in the control of hypertension. While not entirely free of toxicity, these drugs produce few disturbing side-effects. In addition, they have a relatively flat dose response curve in the therapeutic range. This permits fairly uniform dose schedules, which is an important feature of drugs used in general practice. Finally, they have the valuable characteristic of enhancing the antihypertensive effects of other blood pressure-reducing drugs such as reserpine, hydralazine, guanethidine, and methyldopa. This permits lower and, hence, less toxic doses of the latter drugs.

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Mechanism of antihypertensive effect

Three possible mechanisms have been advanced to explain the antihypertensive effects of the thiazide diuretics. The first two implicate the sodium-depleting effect of chlorothiazide while the third claims that thiazides act by a vasodilator mechanism that is independent of the saluretic effect.

A specific vasodilator effect of chlorothiazide discrete from its natriuretic action was first proposed by Hollander, Chobanian, and Wilkins.[1] Their evidence was based on the observation that normotensive control subjects did not exhibit an antihypertensive effect, despite a similar diuresis, and that the reduction in blood pressure began prior to a significant diuresis. This view received some support by the later discovery of diazoxide, a chemically related benzothiadiazine compound. The

latter agent reduces blood pressure and at the same time induces sodium retention.[2-4]

Further analysis of the hemodynamic effects of diazoxide indicate, however, that its mode of antihypertensive effect is quite different from the diuretic benzothiadiazine compounds. The antihypertensive effect occurs immediately following intravenous injection and is rather transient in contrast to the diuretic compounds which require a longer period to act and then exert a more prolonged antihypertensive effect. Diazoxide appears to be a vasodilator compound since the hypotensive response is associated with an increase in cardiac output and a considerable decrease in total peripheral resistance similar to the action of peripheral vasodilators such as amyl nitrite or nitroprusside.[2,4]

The acute antihypertensive effect of chlorothiazide on the other hand is associated with a decrease in cardiac output, while total peripheral resistance usually increases.[5-7] It thus appears that diazoxide has an immediate vasodilator action which seems to be minimal or absent in chlorothiazide.

The argument that chlorothiazide reduces blood pressure prior to a significant saluresis has been disputed by other observers who found that the reduction of arterial pressure occurred only during and after the period of maximum salt loss.[8-10]

Most investigators now agree that the antihypertensive effects of thiazides are related to their ability to produce a sodium diuresis. In fact all drugs which can produce a similar degree of sodium loss will exert a comparable antihypertensive effect such as parenteral mercurials[1] and ethacrynic acid.[11] It is also well known that diets rigidly restricted in sodium will lower blood pressure and will enhance the antihypertensive effects of blood pressure-reducing drugs as well as surgical sympathectomy.[12] However, the manner in which sodium depletion reduces arterial pressure is still in dispute.

There is considerable evidence that the reduction in plasma and extracellular fluid volume which accompanies the diuresis is the important factor in bringing about the initial reduction of blood pressure.[9,13-17] In nonedematous subjects, the diuresis brings about a loss of approximately 2 L. of extracellular fluid volume of which 300 to 400 ml. represent plasma volume.[17a]

The antihypertensive effects of thiazides can be reversed in many patients by re-expanding the plasma volume with salt-free dextran solution[6,9,16,18] or by administering sufficient salt, 15 to 25 Gm. orally per day, to cause a return to control body weight.[13,15]

Depletion of blood volume by even small amounts will enhance the antihypertensive effects of certain agents, particularly of drugs which interfere with sympathetic vasoconstrictor responses.[19] This does not explain, however, how depletion of blood volume by such a relatively small amount could reduce blood pressure in hypertensive patients who are not also receiving other antihypertensive drugs.[20] It is of interest that thiazides do not reduce blood pressure in young normotensive subjects even though they produce a comparable diuresis and depletion of plasma volume.[13]

The reduction of arterial pressure induced by chlorothiazide in hypertensive patients while significant is not of great magnitude.[20] To explain it on the basis of plasma volume depletion, several mechanisms may be considered. The first involves the observation that the pressor response to infused norepinephrine in normal subjects is significantly reduced following diuresis with chlorothiazide or mercurial agents.[21,22] After restoration of plasma volume with salt-free dextran, the blood pressure responsiveness of these normal subjects returned toward and in some cases completely to normal. If the fall in plasma volume (and possibly tissue pressure) diminishes reactivity to any pressor stimulus, then chlorothiazide would also diminish the response to the unknown pressor mechanism which produces essential hypertension. Thus, thiazides reduce blood pressure when an abnormal hypertensive stimulus is in operation. Pressor responses of all types are dampened or diminished.

A second explanation for the moderate depressor effect of relatively small decrements in plasma and extracellular fluid volumes in hypertensive patients involves the baroreceptor mechanism. With aging and hypertension, homeostatic adjustments to either depressor or pressor stimuli tend to become less brisk and effective.[23,24] Mod-

erate decreases in plasma and extracellular fluid volumes are not completely balanced by compensatory vasoconstriction as occurs in young normal subjects. It is pertinent in this regard that elderly normotensive subjects also show some reduction of arterial pressure following thiazide-induced diuresis.[25] Such faulty buffering of blood pressure may be due to reduced compliance of the aorta and carotid artery which occurs with aging and hypertension since the baroreceptor nerves are stimulated by stretching of the arterial wall. Thus, three possible mechanisms have been invoked to support the "volume" theory of blood pressure reduction produced by thiazides, as follows: (1) enhancement of depressor agents or stimuli, (2) damping of pressor stimuli resulting from plasma volume reduction, and (3) reduced baroreceptor responsiveness of hypertensive patients to such volume depletion.

The third explanation that has been advanced to explain the antihypertensive effects of thiazides also involves sodium loss. However, in this case the loss of sodium is said to reduce arteriolar constriction either by "dehydrating" the arteriolar walls or by affecting the concentration gradient of extracellular to intracellular sodium. The latter theory was advanced by Friedman, Nakashima, and Friedman.[26] Tobian *et al.*,[27] however, could find no change in the electrolyte composition of small arterial walls nor of their water content after chlorothiazide. No changes in the electrolyte concentration of the tissues could be found by other investigators either in intact[28] or nephrectomized[29] animals following this drug. This is not surprising since the early studies in man indicated the excreted sodium was derived from extracellular fluid and that water and sodium chloride were lost from that space in isotonic proportion.[17a] Thus, although these theories are attractive in their simplicity there is little objective evidence to support them.

There has been much discussion concerning the difference between the long-term and the short-term effects of thiazides. Whereas, Conway and Lauwers[31] found plasma and extracellular fluid volume depletion in the first week of treatment with chlorothiazide, these were found to return to normal after one month of treatment despite continued reduction of blood pressure. They also found cardiac output reduced after one week but normal after one or more months of continued treatment. For these reasons, they postulated that the thiazides act by some mechanism other than volume depletion during long-term therapy. Since body weight was reduced in their patients despite return to normal of the extracellular fluid volume, they postulated that there was a reduction in intracellular fluid volume during long-term treatment which might play a part in the continued reduction of blood pressure.

Wilson and Freis[17a] also found a return of plasma and extracellular fluid volumes toward but not entirely back to control levels. Body weight returned in equal proportion to extracellular fluid in contrast to the observations of Conway and Lauwers.[31] On withdrawal of chlorothiazide after four to eight months of treatment Wilson and Freis[17a] observed an overshoot of body weight, extracellular fluid, and plasma volumes to above control values. Blood pressure, however, did not rise entirely to control.

It is apparent from studies of the long-term hemodynamic effects of other antihypertensive agents that considerable modification of the initial drug action takes place with time, even though the blood pressure remains reduced. Thus, the reduction of cardiac output found in the initial period of guanethidine treatment disappears with continued treatment, and the hypotension is now due to a reduced total peripheral resistance.[32] Hydralazine initially increases cardiac output which later returns to normal during long-term therapy.[33] Similarly, the abnormalities in plasma volume and extracellular fluid space become modified after long-term treatment with chlorothiazide, but they are not entirely reversed even at six months according to the chronic studies carried out by Wilson and Freis.[17a] Strong evidence that the drug's basic action has not changed is provided by the prompt increase in these fluid compartments when chlorothiazide was discontinued.

Instead of searching for an alteration in fundamental drug action with time, it may be preferable to attempt to clarify the nature of the change in the hypertensive process which produces the return to nor-

mal hemodynamic conditions regardless of the type of agent used.

Toxic effects of benzothiadiazines

Hypokalemia is the most frequent side-effect produced by thiazide treatment. Despite initial concern about potassium deficiency, there has been no clinical evidence of renal damage or other serious manifestations of depletion of body potassium even in patients treated continuously for over five years with thiazides. Total exchangeable potassium remains unaltered during long-term treatment in man[34,35] or animals.[36] Thus, despite an initial moderate kaluresis, both clinical and experimental evidence suggests that the hypokalemia probably represents a disturbance in the potassium gradient between the extracellular fluid and tissue cells rather than a serious depletion of the body's stores of potassium.[13] Clinically, the hypokalemia has little significance except in the potentiation of digitalis toxicity.

The mechanism of the reduced serum potassium is not clear. The principal site of action of the drug appears to be at the proximal renal tubules, whereas potassium excretion occurs primarily in the distal tubules. The salt loss is said to stimulate the production of renin, which would, in turn, increase aldosterone production with possible kaluretic effects.[37] Moderate elevation of carbon dioxide-combining power can occur with thiazide administration, and metabolic alkalosis can cause a migration of potassium ions into cells.

Another common side-effect is hyperuricemia as was first pointed out by Laragh, Heinemann, and Demartini.[38] They found that while large parenteral doses were uricosuric, the customary oral doses blocked the renal tubular transport mechanisms for urate.[39] It is apparent clinically that gout is aggravated by benzothiadiazines and possibly may be caused by the drug. The hyperuricemic effect of the thiazides is readily overcome by probenecid or by allopurinol, the latter drug being especially effective in this regard.[40]

The development of hyperglycemia in occasional patients receiving thiazide drugs was first pointed out by Finnerty.[41] Carbohydrate tolerance tests carried out by Shapiro, Benedek, and Small[42] in thiazide-treated elderly hypertensive subjects indicated that further impairment of carbohydrate metabolism occurred in "potential diabetics" as judged by family history and prior glucose tolerance tests but not in "nondiabetic controls." No change in insulin requirement was found in a series of female diabetic patients who received chlorothiazide throughout the course of pregnancy.[43] These patients received supplemental potassium and also did not exhibit hypokalemia while under treatment. Others have found increases in blood sugar, especially postprandial blood sugar.[44-46] Although Wolff *et al.*[44] believed that permanent diabetes may be produced by thiazides in nondiabetic patients, others have found that the hyperglycemia is reversible on stopping the drug.[45,46] In the Veterans Administration Cooperative Study on Antihypertensive Agents the incidence of diabetes was no higher in the group receiving chlorothiazide than in patients treated by other means.[47] The burden of evidence indicates that while thiazides may reduce carbohydrate tolerance, this disturbance is reversible and probably does not lead to diabetes in nonprediabetic patients.

It is possible that the hyperglycemic effect of the thiazides is related to hypokalemia. The hyperglycemic effect of thiazides in both rats[48] and man[49] has been successfully combated by the administration of potassium supplements. Potassium depletion produced by ion-exchange resin resulted in a decrease in carbohydrate tolerance.[50] There is some evidence to suggest that hypokalemia may reduce the production of endogenous insulin.[50,51]

Other toxic effects which have been ascribed to the benzothiadiazine compounds but which are quite uncommon are dermatitis,[52] thrombocytopenic purpura,[53] and pancreatitis.[54]

Summary

Benzothiadiazine drugs enhance the antihypertensive effectiveness of other blood pressure-reducing drugs in man. In the absence of such drugs the antihypertensive effect of benzothiadiazine is of mild degree. The mechanism of the hypotensive action is associated with sodium loss and appar-

ently not to any direct vasodilator effect. Plasma and extracellular fluid volume reduction, secondary to the sodium depletion, explains part if not all of the antihypertensive effect.

The principle side-effects of thiazide administration are hypokalemia apparently without significant depletion of body stores of potassium, hyperuricemia due to interference with renal tubular transport mechanisms for urate, and reduced carbohydrate tolerance.

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